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Understanding and predicting a complex behaviour using n-of-1 methods: Photoprotection in xeroderma pigmentosum

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Abstract

Objective: Xeroderma pigmentosum (XP) is a very rare inherited disease; the most important aspect of clinical management is rigorous photoprotection from ultraviolet radiation. The aims of this novel study were to: (1) understand and categorize the behavioural complexity and within-participant variability in photoprotection of the face in XP; (2) determine the predictors of photoprotection; and (3) identify individual needs for personalized interventions.

Methods: A total of 20 adults with XP completed an ecological momentary assessment (EMA) study over 50 days. Measures included a UVR diary of photoprotective behaviours used at each outdoor occasion (e.g., hat, face visor, sunscreen), and a mobile phone survey assessing self-reported protection (0-100), satisfaction with protection achieved, and predictive variables (e.g., motivation, effort, mood). Descriptive statistics for photoprotective behaviour were computed, per person. When possible, individual dynamic logistic regression models were used to investigate the predictors of photoprotection, and correspondence between self-reported protection and behaviour.

Results: Photoprotection (clothing and sunscreen) was sub-optimal for most participants, and discrepancies between self-reported protection and behaviour were identified. Modelling of photoprotection was conducted for six participants who went outside sufficient times and used varied protection. Different predictors were identified across participants. Weekend vs. weekday, physical symptoms, stress, and feeling self-conscious were most frequently associated with protection.

Conclusion: The findings support the need for intervention and have implications for the selection of individually-tailored behavioural outcomes and intervention targets to improve photoprotection. The method of profiling multiple preventive behaviours using EMA may be of use in other rare conditions involving complex behaviours.

Key words: xeroderma pigmentosum; rare disease; photoprotection; adherence; n-of-1; ecological momentary assessment

Introduction:

Xeroderma pigmentosum (XP) is a very rare autosomal recessive disorder of DNA repair (Fassihi et al., 2016). It has a prevalence of roughly 2.3 per million live births in Western Europe (Lehmann, McGibbon, & Stefanini, 2011), which equates to just over 100 patients in the UK with a known diagnosis. XP affects men and women equally and has been observed across all continents and racial groups (Fassihi, 2013). Individuals with XP have a defect in the system responsible for repairing DNA damage caused by exposure to ultraviolet radiation (UVR) in daylight, for which there is no cure (Fassihi et al., 2016). There are eight distinct subtypes or 'complementation groups' (XP-A to XP-G, and XP-V or variant), each associated with a defect in a different part of the UVR repair pathway (Fassihi et al., 2016). Symptoms can include extreme sunburn reactions in response to even very low levels of ultraviolet light, and a 2000-fold increase in the incidence of melanoma skin cancers (10,000-fold increase in non-melanoma skin cancer), which frequently start in childhood, as well as progressive and fatal neurodegeneration (which causes cognitive impairment from an early stage), all of which vary according to the subtype (Bradford et al., 2011). Morbidity and mortality in XP are high, and heavily related to UVR exposure. The median life expectancy is 32 years, with premature death largely being caused by skin cancer (metastatic melanoma) or the neurodegenerative disorder, the latter of which is determined by the subtype rather than UVR exposure (Bradford et al., 2011). Rigorous photoprotection in daylight, regardless of environmental factors such as the time of year or weather, therefore plays a crucial role in patient prognosis.

It is recommended that individuals diagnosed with XP reduce overall UVR exposure (e.g., by shifting outdoor activities to times when UVR is lower) and achieve complete coverage of the skin when outside, by wearing tight weave clothing including long trousers and sleeves, gloves, SPF-50 sunscreen, and protecting the face and eyes (Tamura, DiGiovanna, Khan, & Kraemer, 2014). The 'gold standard' of protection involves wearing a face visor, an item of clothing made from plastic that covers the whole face and neck to prevent both UVR from above and reflection from below, and which successfully blocks >99% of UVR. However, many adults are unwilling to do so. The 'next best'

form of protection to a visor includes wearing a wide-brimmed hat, UV-treated glasses (whether sunglasses or clear), a scarf or face-buff pulled up over the mouth, nose, and cheeks, and a hoodie worn up. Patients are encouraged to layer their clothing options to achieve more complete protection (Tamura et al., 2014).

While the genetic causes and symptomatic sequelae of XP are well-understood and researched (e.g., Fassihi et al., 2016; Lehmann et al., 2011), there have been no studies examining whether patients with XP achieve the extreme level of photoprotection recommended, how they combine the different photoprotective behaviours, the stability or variation of behaviour, or the level of protection afforded by these behaviours. Prior to determining the correlates of a particular target behaviour, or any attempts to change behaviour to reduce risk and negative health outcomes, it is first necessary to fully understand the behaviour (Ajzen, 1991; Michie, Atkins, & West, 2014). This is particularly so for uncommon and under-researched conditions and behaviours (Sainsbury, Walburn, Araujo-Soares, & Weinman, 2018), and involves having a clear definition, an understanding of the characteristics and potential subtypes, and the parameters or constraints within which the behaviour may be enacted and vary – for example, who, what, when, where, and how the behaviour is performed. Characterising the photoprotection behaviours used in XP was therefore the first aim of this study.

Research in other populations at increased risk of skin cancer (e.g., skin cancer survivors) indicate that protection is often inadequate (Nahar et al., 2016), in common with poor sun protection in the general population (Kasparian, McLoone, & Meiser, 2009). Predictive and intervention research in these populations may offer some insights into photoprotection behaviour; however, differences in the type and intensity of protection needed and the consequences of non-protection in XP necessitate the conduct of in-depth research specifically in this population (Sainsbury et al., 2018). Further, while research in similar populations is more extensive than in XP, the absence of high quality and effective long-term interventions (e.g., Persson et al., 2018; Rodrigues, Sniehotta, & Araujo-Soares, 2013; Wu et al., 2016) suggests that similar research gaps

also exist within the wider literature. Due to the very small and heterogeneous population of people living with XP, between-participant designs are not a feasible means to investigating photoprotection behaviour or its predictors. Instead, quantitative n-of-1 designs, using ecological momentary assessment (EMA), provide opportunities for capturing within-participant variation in behaviour and over time and contexts, identifying predictors for single cases, and thereby for informing personalized interventions (McDonald, Quinn, et al., 2017; Sainsbury et al., 2018; Vieira, McDonald, Araujo-Soares, Sniehotta, & Henderson, 2017).

This study is part of a UK National Institute of Health Research-funded mixed-methods project with the overarching aims of identifying the reasons for non-adherence to photoprotection recommendations in people diagnosed with XP, and to design, implement, and evaluate a series of psychological interventions to improve photoprotection in a group of non-adherent adults with the condition (Walburn, Sarkany, et al., 2017). The aims of this sub-study were to: (1) describe and categorize the within-participant variability in the behaviours (staying indoors, wearing protective clothing, and applying sunscreen) and combinations of behaviours used to protect the face from UVR in a sample of adults with XP, using an observational n-of-1 design; (2) determine the predictors of photoprotection behaviour; and (3) identify individual needs for personalized interventions. We were specifically interested in photoprotection behaviours relevant to the face, as this is the area of the body most susceptible to skin cancers due to the difficulty of achieving full coverage (Kraemer, Lee, Andrews, & Lambert, 1994). A final aim was to outline a method for profiling multiple preventive behaviours measured over time using EMA, which could be applied to the study of other similar complex behaviours.

Methods:

Participants and recruitment:

The participants were purposively recruited by a research nurse from the caseload of the UK national XP clinical service at St Thomas' Hospital, London (total population = 93 patients at study commencement). For this study, patients were eligible for inclusion if they were adults aged over 16

years, with a laboratory-proven diagnosis of XP, based on the laboratory finding of reduced unscheduled DNA repair in cultured fibroblasts (n = 66), without neurodegeneration (n = 43, including 26 men and 17 women), and with an adequate level of English (n = 38). All participants had consented to participating in the broader study (Walburn, Sarkany, et al., 2017), which involved a total of 69/78 eligible and invited participants (47 mixed-methods + 22 cross-sectional survey only), including children, adults with cognitive impairment, and their respective parents/carers, and which involved also completing qualitative interviews, a cross-sectional survey, using a wrist-worn dosimeter to objectively measure UVR in the environment, and undergoing cognitive testing. All 25 adults without neurodegeneration (17 men and 8 women) who were involved in the mixed-methods study were invited for the n-of-1 component, and 21 agreed. The study was approved by the Camden and King's Cross Research Ethics Committee (ref: 15/LO/1395). No incentives were offered for participation/completion and participants were assured that their decisions would not affect their clinical care.

Design and procedure:

Detailed methods for this study and the broader mixed-methods project have been described elsewhere (see Walburn, Sarkany, et al., 2017). Each n-of-1 study used an observational EMA design in which participants were asked to complete the same measures every day for a 50-day period in the UK spring-summer months (May-August, 2016). The 50-day duration was chosen to provide the minimum 50 observations (assuming individuals went out at least once per day) suggested to conduct the planned statistical analysis (described later), although estimating sample size in an n-of-1 study is difficult in the absence of prior knowledge on the extent of variability in outcomes (McDonald, Quinn, et al., 2017; Vieira et al., 2017). The study was conducted in spring-summer, when days are longest and UVR highest, to maximize detection of variation and inadequacies in behaviour and when barriers to adequate protection are likely to be more salient (e.g., due to mismatches between the need for layered protection and social clothing norms and comfort in the warmer weather vs. winter when such behaviour is more typical).

Daily data collection involved a short online survey completed on the participant's mobile phone and a paper-based UVR protection diary to report their UVR protection behaviour. Text messages containing a link to the survey were sent each evening, at the participant's preferred time, using SurveySignal (Hofmann & Patel, 2015), a programme designed for EMA data collection that links to the online survey software, Qualtrics (Qualtrics, 2017). Completion of the survey took 3-4 minutes; and a reminder to complete the UVR protection diary was included with the thank you/confirmation message that appeared when a survey was submitted. At the end of the 50 days, if the mobile phone survey had not been completed every day, participants were asked to continue completing it and the daily UVR protection diary for a maximum of 5 extra days to increase the number of observations for analysis. Extension of the initial study period, albeit much longer than was requested here (from 2-months to 6-months vs. an extra 5 days), was deemed acceptable to participants in a previous n-of-1 study (Kwasnicka, 2015).

Measures:

The mobile phone survey was purpose-designed to assess self-reported protection (0-100: 'none' to 'complete') and a range of putative predictors. Several iterations of the survey were reviewed by the public and patient involvement (PPI) team (comprised of patient and parent representatives, XP support group members, and a school teacher who has taught several students with XP), and changes to wording and reading level were made, as appropriate. The final version contained 22-items, each measuring a separate sub-construct. Each question was presented in a slider format, which was answered by moving the finger to the position on the 0-100-point line that represented their answer.

The absence of prior research (theoretical or otherwise) in XP to guide decision-making meant that decisions about the included items were informed by other relevant sources, and adaptations to standard theory-based formative research guidelines were necessary (Sainsbury et al., 2018). This approach is also consistent with the contention that a 'one-size-fits-all' theory (and, therefore, intervention) is unlikely to explain the complexity involved in most adherence behaviours

(Easthall & Barnett, 2017; Holmes, Hughes, & Morrison, 2014). Firstly, the constructs and theories applied in previous studies of photoprotection in similar at-risk populations such as skin cancer survivors (e.g., Diao & Lee, 2014) and the general population (e.g., Bränström et al., 2010) were reviewed. Identified constructs here included motivation, beliefs and attitudes regarding risk perception and personal susceptibility, perceived benefits and barriers to protection, positive attitudes towards tanning, and uncertainty about the effectiveness of protection and causes of melanoma. Theories that had been applied in the context of adherence behaviours in chronic illness populations, such as the theory of planned behaviour (e.g., Rich, Brandes, Mullan, & Hagger, 2015), COM-B (e.g., Jackson, Eliasson, Barber, & Weinman, 2014), and the necessity and concerns framework (e.g., Horne et al., 2013) were also reviewed. In addition, a systematic review of constructs specifically relevant to behavioural maintenance, which included motivation, personal resources, self-regulation, habits, and contextual influences (Kwasnicka, Dombrowski, White, & Sniehotta, 2016), and the theoretical domains framework, which contains a wide collection of constructs in common to multiple theories (Cane, O'Connor, & Michie, 2012), were consulted. Finally, the themes that emerged from preliminary analysis of the qualitative interview data from the wider project (e.g., stigma, feelings of self-consciousness and missing out, and social support; Anderson, Walburn, & Morgan, 2017; Morgan, Walburn, Anderson, Weinman, & Sarkany, 2017; Walburn, Morgan, Anderson, Weinman, & Sarkany, 2017), and the expertise of the clinical team (e.g., risk perception and weather) were considered for inclusion (Sainsbury et al., 2018).

The comprehensive, multi-source review process resulted in the inclusion of items to measure self-regulatory (the degree of effort and thought, extent of experienced barriers, and level of planning); environmental and contextual (risk perception, how sunny it was, and physical symptoms); cognitive-emotional (negative thoughts, feeling self-conscious or that they were missing out, stress, mood, quality of life, mental exhaustion, level of activity or arousal); and motivational predictors (motivation, confidence, and importance), as well as social support and satisfaction with the level of protection achieved. All constructs were assessed using single-items, as is typical in EMA

studies of similar duration, to reduce participant burden (e.g., Hobbs, Dixon, Johnston, & Howie, 2013; Kwasnicka, Dombrowski, White, & Sniehotta, 2017; McDonald, Vieira, et al., 2017). These same studies were consulted to suggest item wording for previously measured constructs in other behaviours (e.g., importance, motivation, confidence, stress, mood, activity level, social support).

Most of the questions were asked every day, whereas a subset were asked only on days when the participant indicated that they had been outside (see Supplementary Material for the full list of items). Similarly, some items were anchored specifically to UVR protection when outside (e.g., feeling self-conscious, missing out, social support, effort, and barriers), whereas others were asked about generally (e.g., mood and mental exhaustion). Motivation, confidence, importance, and planning were asked every day in relation to their anticipated UVR protection when outside *tomorrow*, as these constructs show prospective rather than retrospective relationships with behaviour. All other items required participants to retrospectively reflect on their experiences of that day.

The daily UVR protection diary (Walburn, Sarkany, et al., 2017) was based on an adapted version of the UK Office of National Statistics Time Use Survey (Gershuny, 2011). It was developed iteratively in several stages in consultation between members of the research, clinical, and PPI teams. The final version can be found in the online supplementary material. Participants indicated, by drawing a line on the grid: (1) the times of day that they were outside (between 6am and 10pm, the hours of daylight in the UK summer); (2) the clothing items they wore to protect their face from UVR at those times; and (3) when they applied sunscreen to their face (SPF-50, supplied to all patients at the start of the study).

For simplicity, outside time included the duration of time spent outside a building, even if this involved going in and out several times within the one longer period (e.g., in and out of shops or on and off a bus would be counted as one continuous occasion). The protective clothing items listed were face visor, hat, glasses (either sunglasses or clear glasses, treated with a UVR protective coating), scarf or face-buff, and hoodie. These corresponded to the forms of protection

recommended by the XP clinical team to all patients diagnosed with XP[1]. A mobile phone version of the daily UVR protection diary was piloted; however, feedback from the PPI team suggested that a one-page paper copy was easier to comprehend than the >90 questions required to obtain the same information in the online format (due to the need to record information at 15-minute intervals over 16 hours and for seven behaviours). In contrast, the use of the mobile phone survey for the EMA questions was considered simpler and likely to be more reliably recorded electronically than on paper.

The daily photoprotection scale (DPS) was developed in consultation with the clinical team to rank and categorize the relative protection afforded by each photoprotection behaviour/combination (excluding sunscreen), as recorded in the daily UVR protection diary (see Table 1 and online supplementary material for details).

Table 1. Daily photoprotection scale (DPS)

Photoprotection behaviour	**Protection category**
1. No protection	None
2. Hoodie OR scarf/buff OR glasses	Very poor
3. Glasses + scarf/buff 4. Glasses + hoodie 5. Scarf/buff + hoodie	Poor
6. Hat 7. Hat + hoodie 8. Glasses + scarf/buff + hoodie	Moderate
9. Hat + glasses 10. Hat + glasses + hoodie 11. Hat + scarf/buff 12. Hat + scarf/buff + hoodie	Good
13. Hat + glasses + scarf/buff 14. Hat + glasses + scarf/buff + hoodie	Very good
15. Face visor	Excellent

Note: The use of sunscreen was not included in the combinations – instead, behaviours were ranked assuming that sunscreen was a constant (i.e., that it was used with every behaviour or not used with any behaviour).

[1] The use of Dermagard window films (a clear window coating that blocks 99.8% of UVR) when travelling in a car was not included in the diary.

N-of-1 data preparation and statistical analysis:

The data from the daily mobile phone surveys for each participant were downloaded from Qualtrics into separate excel spreadsheets. The paper-based daily UVR protection diary data for each participant were manually entered into a pre-designed spreadsheet by the research nurse and a research assistant, and were checked for accuracy. Using R version 3.2.5 (R Development Core Team, 2008), the behaviours/combinations used at each outdoor occasion were mapped to the DPS (behaviour and category) from the raw data. It is recommended to all XP patients when they visit the clinic that they re-apply SPF-50 sunscreen every 2-3 hours when outside. For the purposes of analysis, the protection associated with each application was therefore carried over for 3 hours (12 x 15-minute blocks). Any time spent outside where sunscreen had not been applied in the last 3 hours was coded as 'not protected' on this variable. Time of day for each outdoor occasion was coded as either high-risk (11am-3pm) or lower-risk (either side of 11-3; note, there is always a level of risk for XP patients); outdoor occasions were coded according to the day of the week (weekday vs. weekend).

Descriptive statistics are provided for five behaviour-relevant outcomes: (1) DPS photoprotection behaviours; (2) DPS photoprotection categories; (3) use of sunscreen; (4) self-reported photoprotection; and (5) satisfaction with the level of photoprotection achieved. For the first 3 protection variables, all derived from the daily UVR protection diary, analysis is limited to the time spent outside (i.e., photoprotective behaviours used when indoors were not analysed). The proportion of outdoor occasions for which each DPS behaviour and photoprotection category were used was calculated per person. Based on the observation that many participants changed their photoprotective behaviours (and therefore level of protection achieved) midway through an outdoor occasion, descriptives for total outdoor time and the first 15 minutes of each outdoor occasion are provided. To capture whether the behaviours used in the first 15 minutes (i.e., behaviour initiation) were used for the whole duration of each outdoor occasion (i.e., maintenance), descriptive statistics, including the direction of the change are also provided.

For sunscreen, the total number of 15-minute blocks spent outside over the study period was calculated for each participant, and the number of blocks for which they were protected by sunscreen was expressed as a percentage of this. Information about non-protected times was summarized to indicate whether participants were not applying sunscreen at all for some outdoor occasions, or whether they were applying but not re-applying frequently enough if an outdoor occasion lasted for longer than 3 hours. For self-reported photoprotection (0-100), the median, inter-quartile range (IQR), and minimum and maximum ratings are summarized for each participant. Spearman's rho was used to compute the relationship between self-reported protection and satisfaction with protection, for each participant.

Descriptive statistics for photoprotection behaviour (DPS behaviours and categories) were computed based on all data provided in the daily UVR protection diary, regardless of whether the mobile phone survey had also been completed on those days; likewise, descriptive statistics for self-reported protection and satisfaction were based on all data from the mobile phone survey (only answered on days when the participant went outside). For analyses concerning the combination of these data sources, only days for which both were completed could be included.

A threshold of at least 50 outdoor occasions was set as the criteria for statistical modelling of photoprotection (McDonald, Quinn, et al., 2017; Tabachnick & Fidell, 2007; Vieira et al., 2017). In addition, there needed to be sufficient variability in both photoprotection (DPS) and predictors (EMA questions). The main outcome for the n-of-1 analyses was the level of photoprotection according to the DPS categories, which were dichotomized for each person to reflect their 'best' protection (highest category of protection used on at least 10 occasions over the study period) versus the rest. This decision was based on the non-normal distribution of DPS behaviours for most participants, which, combined with the ordinal nature of the scale, meant that using the data continuously was inappropriate. The use of a dichotomous outcome is consistent with a recent study in physical activity behaviour where analyses also involved using dynamic logistic regression (McDonald, Vieira, et al., 2017). The relationship between self-reported protection and DPS protection category used in

the first 15-minutes of each outdoor occasion was analysed using dynamic logistic regression (Vieira et al., 2017). For participants with limited or no variability in either DPS categories or self-reported photoprotection (0-100), visual inspection was used to assess the likelihood that their self-report represented an over- or under-estimation of protection.

Dynamic logistic regression was also used to assess relationships between DPS categories and: (1) sunscreen use; (2) temporal factors (11am-3pm vs. other; weekday vs. weekend, respectively); and (3) each EMA variable. Dynamic modelling adjusts for autocorrelation by incorporating the dependence of future on past. This is achieved by including lagged covariates, representing the history of the predictors of interest (e.g., psychological variables) and the outcome (i.e., photoprotection behaviour), in conventional multivariable regression models (Vieira et al., 2017). The analysis was not only adjusted for time-trend (study day) and the order of multiple outdoor occasions within the same day, but the past behaviour (DPS category) and EMA assessments for the previous two outdoor occasions for each participant were included. In the absence of prior research in XP to inform a power analysis (i.e., anticipated effect sizes or sample size, which represents the number of observations per participant rather than the number of participants), a *p*-value threshold of <.07 was adopted to indicate statistical significance. While this value is somewhat atypical, an inclusive position was adopted so as not to miss an effect that may have meaningful implications for intervention decisions and/or emerge as significant if more observations were obtained.

Results:

Twenty-one adults were recruited; one discontinued responding to the survey after 5 days and was excluded from the analysis. Descriptive analyses are based on 14 men and 6 women, with a mean age of 40.7 years (standard deviation (SD) = 15.7, range = 16-63), and who had been clinically diagnosed with XP between the ages of 2 and 53 years (M = 23.0, SD = 15.7). This included patients with extreme sunburn reactions (n = 6; XP-A, XP-F) and those without abnormal sunburn reactions (n = 14; XP-C, XP-E, and XP-V).

Study completion

Participants completed the daily UVR protection diary for between 18 and 57 days, and the mobile phone survey for between 20 and 51 days; the number of matched days (i.e., when both were completed) ranged from 18-51. Of the 20 participants who provided daily UVR protection diary and/or EMA data for full the duration of the study (i.e., across 50 days, although with some missing days), five went outside on too few occasions (5-45 times) to enable statistical modelling (see Figure 1). A further eight had limited variability in photoprotection when outside, and one participant had limited variability in all EMA questions. The n-of-1 statistical methods could therefore only be applied to six participants. Descriptive statistics for behaviour will be provided for all 20 participants (denoted in text using participant IDs: 001-020), followed by the modelling of photoprotection for those six participants (denoted in descriptives tables using *).

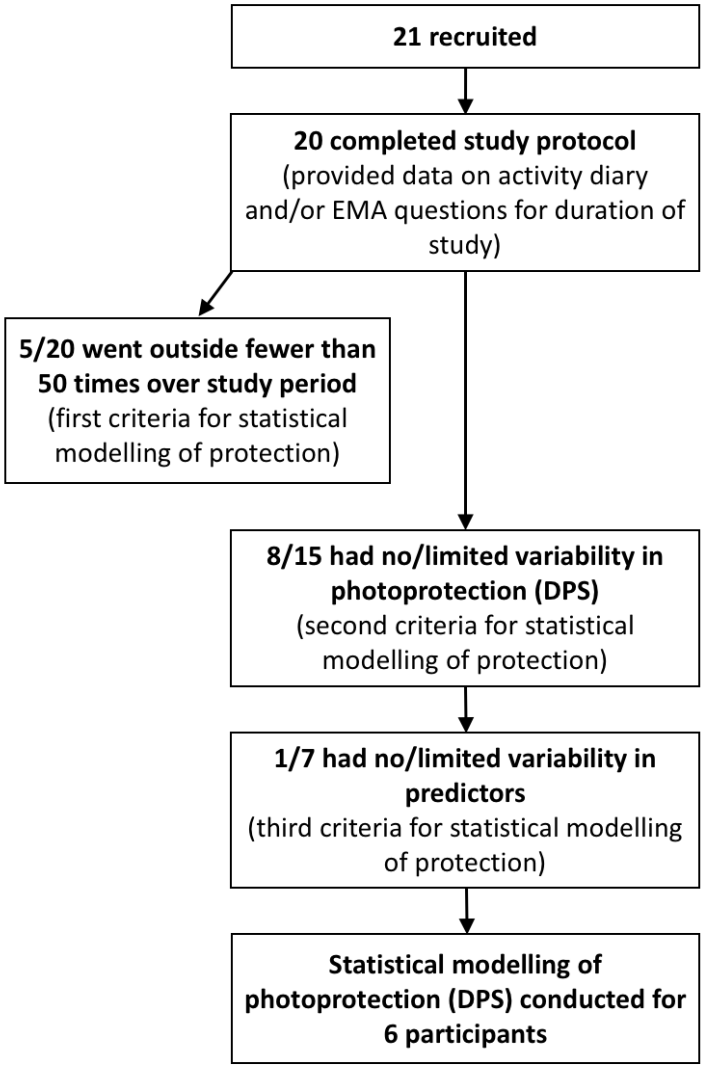

Figure 1. Flowchart of study completion and eligibility for statistical modelling of photoprotection

Time spent outside

The number of times participants went outside for more than 15-minutes ranged from 5 (on average, once per week) to 153 (on average, 3 times per day) over the completion period (see Table 2). The median time spent outside ranged from 15 minutes to 2 hours. For all participants, the minimum time spent outside on one occasion was 15 minutes (the smallest interval recorded on the daily UVR protection diary), while the maximum time spent outside ranged from 2 to 14 hours. Of the five participants with limited outdoor occasions, three had a subtype of XP associated with an abnormal sunburn reaction.

Table 2. Time spent outside

Participant	Days (UVR diary)	No. outdoor occasions	Median interval (time)	Range	Lower quartile	Upper quartile
001	48	5	4 (1h)	1-9 (2h,15m)	2 (30m)	6 (1h,30m)
002	49	12	3 (45m)	1-8 (2h)	2 (30m)	4 (1h)
003	18~	14	8 (2h)	1-17 (4h,15m)	4 (1h)	12 (3h)
004	50	16	6 (1h,30m)	1-28 (7h)	3 (45m)	13 (3h,15m)
005	48	45	7 (1h,45m)	1-43 (10h,45m)	2 (30m)	13 (3h,15m)
006	50	68	3 (45m)	1-18 (4h,30m)	2 (30m)	6 (1h,30m)
007	49	71	5 (1h,15m)	1-29 (7h,15m)	3 (45m)	9 (2h,15m)
008	49	79	7 (1h,45m)	1-36 (9h)	2 (30m)	14 (3h,30m)
009	54	93	4 (1h)	1-56 (14h)	2 (30m)	8 (2h)
010*	50	95	5 (1h,15m)	1-27 (6h, 45m)	2 (30m)	8 (2h)
011*	52	104	2 (30m)	1-25 (6h,15m)	1 (15m)	4 (1h)
012	56	105	7 (1h,45m)	1-40 (10h)	3 (45m)	13 (3h,15m)
013*	50	112	1 (15m)	1-12 (3h)	1 (15m)	3 (45m)
014*	55	113	5 (1h,15m)	1-48 (12h)	2 (30m)	11 (2h,45m)
015*	57	117	4 (1h)	1-48 (12h)	2 (30m)	11 (2h,45 m)
016	53	117	2 (30m)	1-18 (4h,30m)	1 (15m)	4 (1h)
017	57	119	5 (1h,15m)	1-37 (9h,15m)	2 (30m)	10 (2h,30m)
018	50	132	3 (45m)	1-26 (6h,30m)	1 (15m)	6 (1h,30m)
019	52	145	3 (45m)	1-28 (7h)	2 (30m)	6 (1h,30m)
020*	57	153	6 (1h,30m)	1-48 (12h)	2 (30m)	14 (2h,30m)

Note: participant ID numbers were re-assigned for publication to ensure anonymity (ordered here by ascending number of outdoor occasions); each interval is equivalent to 1 x 15-minute block, as recorded in the daily UVR protection diary; ~003 only completed daily UVR protection diary for first 21 days (with 3 missing days) but completed n-of-1 questions for 51 days; * denotes the 6 participants for whom statistical modelling of photoprotection was possible (see Table 4).

Behaviours and protection categories

Across participants, almost all photoprotection behaviours from the DPS were reported. Participants reported using between two and ten different clothing combinations when they went outside over the course of the study. Most participants (14/20) failed to protect their face from UVR on at least some of the occasions they went outside (see Table 3). Thirteen of the participants were using 'very poor' or no protection during at least 20% of all outdoor time, and this was as high as 40-100% in some participants (≥97% in four participants). Three participants achieved 'very poor' or

‘poor’ protection at best (excluding 0.3% and 0.4% ‘good’ for two of these participants), while another four achieved only ‘moderate’ protection at best. There were only two participants who did not report using any of the five lowest ranking behaviours (corresponding to none, ‘very poor’, and ‘poor’ protection) for any outdoor time.

Four participants, all of whom had a subtype of XP not associated with an abnormally severe sunburn reaction, reported ever wearing a visor, ranging from 8-86% of all time spent outdoors (top line of Table 3), and 11-90% of outdoor occasions (bottom line), when looking only at the first 15-minutes of each occasion. Ten participants reported at least ‘good’ protection (i.e., ‘good’, ‘very good’, or ‘excellent’) 50% or more of the total time spent outdoors. The most commonly reported behaviours were glasses only (‘very poor’), wearing a hat and glasses together (‘good’), or only a hat (‘moderate’). Wearing a scarf/face-buff or hoodie were least commonly reported.

Table 3. Daily photoprotection scale (DPS): Proportion of outdoor time (top line) and outdoor occasions (bottom line) for which each behaviour combination was used, and proportion of outdoor time protected by sunscreen

	None	**Very poor**	**Poor**			**Moderate**			**Good**				**Very good**		**Excellent**	
ID (no. of outdoor occasions)	Not protected	Glasses OR hoodie OR scarf/buff	Glasses + scarf/ buff	Glasses + hoodie	Scarf/ buff + hoodie	Hat	Hat + hoodie	Glasses + scarf/ buff + hoodie	Hat + glasses	Hat + glasses + hoodie	Hat + scarf/ buff	Hat + scarf/ buff + hoodie	Hat + glasses + scarf/ buff	Hat + glasses + scarf/buff + hoodie	Face visor	% time protected by sunscreen
001 (5)	42.1 40.0	57.9 60.0														63.2
002 (12)		8.3 8.3				8.3	60.4 50.0			22.9 41.7						66.7
003 (14)		39.7 42.9		38.7 33.3			21.6 21.4									0.0
004 (16)	1.9 6.3	2.5 6.3		8.8 6.3						34.0 56.3					52.8 25.0	86.8
005 (45)	16.8 20.0	58.5 28.9		19.4 33.3		3.8 15.6	1.5 2.2									
006 (68)	11.1 14.7	73.3 73.5	7.0 5.9	2.9 1.5	3.5 1.5	2.1 2.9										73.6
007 (71)	6.4 1.4	22.1 32.4				11.3 15.5			60.1 50.7							80.1
008 (79)	12.5 8.9								1.6 1.3						85.9 89.9	29.8
009 (93)		1.5 3.2				1.2 2.2			89.7 83.9						7.6~ 10.8~	49.3
010 (95)*	12.1 16.8	1.7 3.2	4.1 3.2			4.2 3.2	1.5 2.1	2.8 2.1	2.2 4.2		1.7 1.1	0.3 1.1	69.4 63.2			73.2
011 (104)*		40.1 42.3							59.9 57.7							54.9
012 (105)						2.4 3.8			65.3 76.2				32.2 20.0			71.5

013 **(112)***	19.6 17.6		6.7 2.7									2.2 0.9	5.0 1.8	66.5 76.8	82.1
014 **(113)***	45.2 25.7	2.3 4.4				52.4 69.9									63.3
015 **(117)***	14.1 18.8	22.5 28.2				1.0 0.9			62.4 52.1						46.4
016 **(117)**									1.7	98.3 100					44.0
017 **(119)**	1.8 5.9	60.4 73.1	36.0 20.2			0.7			1.1 0.8						57.0
018 **(132)**	10.3 13.6	20.4 8.3		68.8 77.3						0.4 0.8					16.6
019 **(145)**	15.3 1.4	84.4 98.6							0.3						45.8
020 **(153)***	35.3 49.0	24.3 26.8				12.6 9.2			26.5 14.4			1.4 0.7			45.7

Note: based on all days for which the daily UVR protection diary was completed (regardless of whether the EMA questions were also completed on that day); shading indicates patient has a diagnosis of a subtype of XP associated with an abnormal sunburn reaction; ~009: all instances of wearing a visor occurred in 2 consecutive days in the middle of the study period; * denotes the 6 participants for whom statistical modelling of photoprotection was possible (see Table 4); sunscreen data was not reported for 005 due to unreliability/inconsistency in completion.

Maintenance of UV protection behaviour within an outdoor occasion

All but two of the 20 participants reported at least one change in photoprotection behaviour, within an outdoor occasion, after the first 15-minutes (range = 0-29% of all outdoor occasions). This meant that the proportion of time that each behaviour was used differed depending on whether the first 15-minutes or all outdoor time was considered. The number of changes within a single outdoor occasion ranged from 1 to 17 (in an outdoor occasion that lasted 5 hours, 45 minutes). Across the sample, there were more instances of changes in photoprotection behaviour resulting in a worse level of protection (i.e., removed a clothing item: 38.2%) than an improvement in protection (i.e., added a clothing item: 21.2%). The remainder (35.8%) involved switching back and forth between several behaviours within the one outdoor occasion (in 4.8% of cases, the change in behaviour did not change the protection category). Most improvements were from either none or 'very poor' protection to some level of protection (ranged from 'very poor' to 'very good'). The reverse was true of worsened protection – most changes in this direction ended with either 'very poor' or no protection. In two participants who wore a visor for at least half their outdoor occasions, most instances of changed protection involved removing the visor after the first 15 minutes.

Sunscreen use and re-application

Sunscreen protection ranged from zero to 89% of all outdoor time (median = 57%; see last column of Table 3). A significant positive relationship between sunscreen and DPS categories was found for 4/6 participants (in whom modelling was possible), indicating that they were more likely to have used sunscreen in combination with their 'best' protection rather than compensating for a lack of other protection by using sunscreen (see first line of Table 4). Participants were protected for the entirety of between 0 and 80% of outdoor occasions (median = 49%; see supplementary Table 1). The other occasions, where at least some of the time participants weren't protected by sunscreen, were divided between those where no sunscreen was worn at all (4-100%; median = 27%) and those where sunscreen was used but not re-applied frequently enough, given the duration of the occasion (0-40%; median = 11%).

Self-reported photoprotection and satisfaction with protection

Median scores for self-reported protection ranged from 28 to 100, although most (16/20) were above 70. Three participants self-reported their photoprotection as 100 ('complete') on every day that they went outside (see online supplementary Table 2). In contrast, six participants perceived that they never achieved this level of protection (i.e., did not have any ratings of 100). In five of these cases, the maximum scores were still relatively high, ranging from 81-95; the last participant rated their protection as 62 every day. Only three participants rated their protection as zero at any point in the study.

It was possible to statistically model the relationship between self-reported photoprotection and satisfaction with protection (both 0-100) for 12 participants (excluding the three who showed no variability in self-reported protection and five who went outdoors on too few days and therefore did not answer these questions on most days). In 9/12 participants, there was a statistically significant positive correlation, indicating that greater satisfaction was associated with higher self-reported protection. The strength of these correlations corresponded to medium-to-very large effect sizes. The correlations for the other three participants were not significant.

Correspondence between self-reported protection and DPS

It was possible to statistically model the relationship between self-reported photoprotection (0-100) and DPS (as recorded on the daily UVR protection diary, and dichotomized into 'best' vs. the rest) for only 5/20 participants (excluding one additional participant due to no variability in self-reported protection; see online supplementary Table 3). In one case, there was a statistically significant and positive relationship, indicating that self-reported protection was greater on days when objectively better protection (in this case, a hat) was used. In the other four cases, the relationship was not significant.

Of those who could not be modelled, visual inspection of the data was used. In 2/4 cases where self-reported protection had a median of 100, the participants used 'good' protection at best, and this represented only 60% of their outdoor time (IDs: 007, 011), suggesting that self-reports

provided an overestimation of protection. The other two participants were using 'excellent' or 'good' protection most of the time, suggesting that their ceiling-level self-reports were more accurate (IDs: 008, 009). Self-reports (median = 94) for the participant who had no variation in DPS category ('good' 100% of outdoor time) also suggested high accuracy (ID: 016).

Of the seven participants with poorest protection when outside (78-100% none, 'poor', or 'very poor'), only two had low median self-reports, suggesting appraisals of their behaviour were relatively accurate (IDs: 003, 018). The other five had higher median self-reports, suggesting that they were *overestimating* their photoprotection (IDs: 001, 005, 006, 017, 019); as was a participant with a median self-report score of 84, despite using 'good' protection only 23% of the time (ID: 002). In contrast, two participants appeared to have *underestimated* their protection, with median scores of 70.5 and 62, respectively, despite using 'good' or 'very good' protection 97.5% of the time (ID: 012) and 'good' or 'excellent' protection 87% of the time (ID: 004).

Statistical modelling of photoprotection

As outlined in Figure 1, it was only possible to model the predictors of photoprotection (DPS 'best' vs. the rest) in six participants. Between three and 10 predictors were identified per person. Whether it was the weekend or a weekday was associated with photoprotection for four participants – in two, protection was better on the weekends, whereas for the other two, protection was better during the week (see Table 4). The degree of noticeable physical symptoms, either in the same occasion (lag 0) or two occasions before (lag 1) was positively associated with photoprotection for three participants; for one of these, *fewer* symptoms on the last outdoor occasion (lag 1) was also associated with better protection. Protection was better during the hours of 11am-3pm (vs. outside this high-risk time) for two participants. Greater perception of risk was also related to better protection for two participants, as was how sunny (sunnier) it was for one of these.

The amount of effort and extent of perceived barriers were related to photoprotection for the same two participants. In both cases, greater effort was associated with better protection, whereas barriers showed an inconsistent relationship whereby better protection was associated

with *more* barriers for one participant and *fewer* barriers for the other. The extent of planning and level of importance placed on protection, two outdoor occasions ago, were related to better current protection for one participant.

More stress on the last outdoor occasion was associated with better protection for three participants. While two participants had better protection when they felt *more* self-conscious (lag 0 and lag 1, respectively), for one participant, protection was better when he felt *less* self-conscious. Feeling more like they were missing out (lag 2) was related to *better* protection for one participant, and to *worse* protection (lag 0) for another participant. Feeling more active and having fewer negative thoughts were each associated with better protection for one participant. More negative mood, poorer quality of life (lag 2), and feeling *less* mentally exhausted on the last outdoor occasion (lag 1) but *more* exhausted currently (lag 0) were each associated with better protection for one participant. Social support, motivation, and confidence were not associated with protection for any of the six participants.

Table 4. Dynamic logistic regression showing associations between predictor variables and DPS photoprotection categories ('best' vs. the rest) for 6 participants for whom modelling was possible

	010 (very good)	**011 (good)**	**013 (excellent)**	**014 (moderate)**	**015 (good)**	**020 (good)**
Sunscreen use	3.14 (1.71, 4.92)***		4.86 (3.04, 7.36)***		1.51 (0.47, 2.66)**	1.31 (0.16, 2.61)*
Weekday/end	-1.98 (-3.88, -0.30)*			-1.43 (-2.72, -0.22)*	2.69 (1.20, 4.69)**	1.46 (0.31, 2.63)*
Time of day (11am-3pm vs. other)					2.38 (0.96, 4.11)**	1.61 (0.03, 3.46)$^{\#}$
Physical symptoms	0.04 (0.01, 0.09)*				0.38 (0.07, 0.80)* -0.42 (-0.84, -0.11)*^{L1}	0.08 (0.01, 0.17)$^{\# L2}$
Risk perception	0.06 (0.02, 0.12)*					0.11 (0.05, 0.19)**
Sunny						0.08 (0.04, 1.43)**
Effort	0.03 (0.00, 0.05)*					0.05 (0.01, 0.09)* -0.04 (-.08, 0.00)$^{\# L2}$
Barriers	-0.11 (-0.23, -0.03)*					0.08 (0.02, 0.17)*
Planning				0.08 (0.01, 0.16)*^{L2}		
Importance				0.06 (0.02, 0.11)**		
Stress	0.02 (0.05, 0.43)*^{L1}	0.17 (-0.01, 0.36)$^{\#L1}$		0.05 (0.00, 0.12)$^{\#L1}$		
Self-conscious	0.15 (0.03, 0.32)*^{L1}	0.22 (0.03, 0.45)*	-0.09 (-0.17, -0.02)*			
Missing out	0.01 (-0.04, 0.06)$^{\#L2}$	-0.16 (-0.34, 0.00)$^{\#}$				
Negative thoughts			-0.04 (-0.09, -0.00)*^{L1}			
Mental exhaustion				-0.05 (-0.10, -0.01)* 0.04 (0.00, 0.08)$^{\#L1}$		
Mood		-0.14 (-0.27, -0.01)*				
Active	0.07 (0.02, 0.14)*					
Quality of life					0.07 (0.01, 0.15)*	

Note: based on 'matched' days (i.e., those where the daily UVR protection diary and EMA questions were completed) and only those on which the participant went outside; descriptor in brackets after each participant number indicates the 'best protection' category; all analyses controlled for study day (time trend), the order of multiple occasions within the one day, and past behaviour (DPS category) and relevant EMA assessment for the previous two outdoor occasions; weekday/end: a positive coefficient indicates that protection was better on the weekend, a negative coefficient indicates that protection was better during the week; time of day coded as 11am-3pm vs. either side of this high-risk time, a positive coefficient indicates protection was better during the high risk time; relationships are based on lag 0 unless otherwise indicated; L1 = lag 1, L2 = lag 2; * $p < .05$, ** $p < .01$, *** $p < .001$, $^{\#}$ $p < .07$

Discussion:

XP is a very rare chronic disease in which affected individuals are reliant on rigorous photoprotection to minimize UVR exposure and preserve their health. Observational n-of-1 designs are well-suited to rare diseases, where previous research is sparse and statistical power limited due to low numbers (Sainsbury et al., 2018). While single case approaches have been applied and recommended in the evaluation of treatments and interventions in rare diseases (Gagne & Kesselheim, 2014), to our knowledge, no previous research has used an observational n-of-1 design to understand a target behaviour prior to intervention design in this way before. Despite the small available participant pool, the recruitment of 21 individuals with XP and the near-completion of the study protocol by all but one demonstrates the feasibility and acceptability of the methodology, which may offer a viable alternative for observational research in other rare and poorly-understood complex conditions.

This study had three main aims, the first of which was to capture the complexity and within-participant variability in photoprotection of the face in individuals diagnosed with XP. The analysis yielded detailed insights into the types, combinations, and stability/variability of photoprotection behaviours used in this population that are far superior to the level that could be obtained using alternate methods. Examining time spent outside and stability, three patterns of photoprotection were identified: the first involved protecting predominantly by staying indoors (i.e., participants went outside fewer than 50 times, which was the threshold for statistical modelling); the second involved more frequent outdoor occasions but with reasonably stable photoprotection behaviours (which also precluded statistical modelling) across those occasions (whether good or poor); and the third involved going outside and using a range of photoprotection behaviours – it was only this latter group for whom statistical modelling was possible. Overall, there was considerable room for improvement in protection when outside, regardless of the frequency of going out and including both sunscreen use and protective clothing, supporting the need for interventions targeted at this

problem. Discrepancies between self-reported protection and adherence to photoprotection recommendations, as well as covariation with satisfaction, further confirm this need.

The second aim of the study was to determine the predictors of photoprotection behaviour. While only the participants who went outdoors and showed variation in protection met the thresholds for statistical modelling, the finding that a different number and pattern of predictors was significant for each participant again supports the usefulness of the single-case approach, as well as the inclusion of different types of predictors drawn from diverse theories and sources, and the planned use of individually-tailored interventions. Several different patterns regarding the ways that significant predictors clustered together were observed; that is, there were differences in the influence that temporal, physical/environmental, and self-regulatory versus cognitive and emotional predictors exerted on behaviour, and the direction of those relationships (e.g., greater barriers were associated with better protection for one person and worse protection for another; a similar pattern was observed for weekdays vs. weekends). Specifically, for one participant, the only predictors of photoprotection behaviour were symptoms (i.e., physical) and the time of day and week (i.e., temporal), while for another, weather, risk perception (i.e., environmental), effort, and barriers (i.e., self-regulatory) were additionally relevant. In contrast, there were two participants for whom the emotional and cognitive factors (e.g., missing out, self-consciousness, stress), but none of the former factors, were significant. Lastly, there were two participants for whom variables across these groups were relevant. When combined with the rich descriptive analysis of behaviour and predictors in all cases, there are numerous implications that can inform intervention design and any tailoring to individual needs in the next phase of this research (the third aim).

Firstly, decisions about the behavioural target and level of improvement suggestive of success will need to be made on a case-by-case basis. For participants who are already using ‘gold standard’ or ‘next best’ protection for part of their outdoor time, the goal will likely include increasing the amount of time these behaviours are used, thereby reducing time with lesser protection. At the other end of the spectrum, for participants who are only achieving ‘good’ or lower

protection at best (deemed inadequate by the clinical team), improvement will almost certainly need to involve the uptake of new behaviours or using existing behaviours in novel combinations (e.g., wearing a hat, glasses, and scarf together rather than separately). Another form of improvement for some participants may be the more consistent use of their chosen photoprotection from the outset and for the whole duration of an outdoor occasion (i.e., as opposed to removing clothing items mid-way through an outdoor occasion), and across time (e.g., high vs. lower risk) and contexts (e.g., weekend vs. week days). Given the large discrepancy with clinical recommendations for some individuals, the magnitude of change possible within the context of a time-limited intervention will also need to be considered.

There were some predictors that were more consistently related to photoprotection across participants (e.g., weekday vs. weekends, physical symptoms, and feeling stressed and self-conscious) than others. Although not using an n-of-1 design, differences in UVR exposure between weekdays and weekends have previously been highlighted (Parisi et al., 2000), indicating the need to tailor intervention strategies to natural temporal variation that exists for many people (e.g., working indoors during the week and spending weekends outdoors, or vice versa). Differences in protection according to the time of day (better during higher-risk time), perceived need for protection, and increased skin symptoms support the observations of the clinical team that risk perception is incorrectly based on environmental factors and symptom-based feedback, when there is no safe level of UVR exposure for people with XP. Interventions should, therefore, include strategies to reduce reliance on changeable and contingent cues for protection, replacing them with cues that can be utilized to trigger protection regardless of variability in their expression (e.g., habit formation based on using protection at the same time and in the same way each day).

The emotional burden of having XP seemed to include feeling stressed, self-conscious, and like they were missing out because of needing to protect from UVR, which were also associated with photoprotection for two or more participants, although the direction of the relationships for the latter two variables differed across participants. Although causality cannot be established, possible

explanations for these relationships include that the absence of negative psychological experiences and the presence of positive ones may prompt good photoprotection. In contrast, negative psychological experiences may also be the consequence of better protection (possibly via the effort and restrictions that good protection entails), and these may, over time, come to act as barriers to protection, while good protection may result in a reduced sense of stress and missing out (as complete protection may enable greater participation in otherwise restricted activities). The role of emotions (anticipated negative mood) in understanding sun protection behaviour, in addition to protection-related cognitions, has been emphasized and suggested as an additional target for intervention (Mahler, 2014). Similarly, amplification of the positive emotion that results from engagement in healthy behaviours has recently been proposed as a mechanism by which motivation and behaviour may be maintained (Van Cappellan, Rice, Catalino, & Fredrickson, 2018). The current results support the importance of considering various interactions between emotion (positive and/or negative) and protection for some patients with XP, with wellbeing and mental health needing to be balanced with the need for good protection.

Neither motivation nor confidence were related to photoprotection for any participant. This contrasts with typical between-participant findings, where both theory of planned behaviour variables are predictive of better sun protection in the general population (Starfelt Sutton & White, 2016). Although likely partially attributable to restricted variability and near-ceiling scores here, this pattern is also somewhat consistent with n-of-1 results in other behaviours. For example, in two studies of physical activity (each with six single-cases), intention and confidence were predictive of behaviour for some but not other participants (Hobbs et al., 2013; Quinn, Johnston, & Johnston, 2013). In the latter study and another study of activity in weight loss maintenance, the direction of the intra-individual effect for confidence was opposite to expectations in at least one case (i.e., lower confidence was associated with more activity; Kwasnicka et al., 2017; Quinn et al., 2013).

In contrast, the predictive value of aspects of self-regulation (e.g., barriers and planning) for some participants is consistent with previous between-participant research in sun protection (Allom,

Mullan, & Sebastian, 2013; Bränström et al., 2010). Differences in findings between within-participant and between-participant designs highlight the risks of potential loss of information associated with extrapolating from studies designed to answer fundamentally different questions, and point to the benefits of n-of-1 research when feasible in small, heterogeneous, and unstudied populations (Sainsbury et al., 2018). Together, these results support the inclusion of strategies to target a wide range of motivational (e.g., importance and risk perception) and volitional (e.g., self-regulatory and emotional) factors, and the tailored selection of intervention materials to match unique participant characteristics and patterns.

Strengths, weaknesses, and unanswered questions

There are several strengths of this study. The comprehensive data collection protocol, single-case analytic approach, recruitment of almost all eligible patients in the UK, and very low attrition rate lend confidence to the findings, as the level of detail obtained could not have been achieved using other quantitative methods in a rare disease. Additionally, although researcher-led, the clinical and PPI teams were involved at all stages, which ensured that the assessments were both acceptable and aligned with what is deemed clinically relevant to patients with XP. The novel method for combining and profiling multiple preventive behaviours over time may be of use in other poorly-understood complex behaviours (e.g., adherence to the multiple drug-based treatments, physical therapies, and dietary behaviours involved in managing cystic fibrosis or diabetes mellitus), which gives this work relevance beyond this specific illness context. Finally, XP has long been used as a model disease to gain key insights into the mechanisms by which skin cancers occur in healthy individuals, because it represents an extreme version of the same process (Kraemer et al., 1994). Similarly, photoprotection in XP can be viewed as an extreme version of the photoprotection required in patients with other photosensitive skin diseases, and in patients at risk of skin cancer. It is, therefore, likely that the findings from this behavioural work can be meaningfully extrapolated to inform intervention development in these other patient groups requiring photoprotection.

There are also a few methodological limitations that should be considered when interpreting the findings. Although the completion of the daily UVR protection diary each day should increase its reliability over one-off retrospective questions, its psychometric utility is still dependent on the accuracy of the self-report and vigilance of the participant keeping it. Because the daily UVR protection diary was completed on paper rather than online, participants may have completed it retrospectively for several days, which would also reduce its reliability. A further limitation may be the lack of correspondence between reports of photoprotection behaviour (i.e., DPS) and the 0-100 self-report rating of protection, although this is an important finding in itself. It may be that by not anchoring the upper endpoint of the self-report item to 'gold standard' protection (i.e., use of a face visor), participants instead answered '100'/'complete' on days when they achieved their personal best protection, and this accounts for some of the discrepancy between the two measures. Research in non-XP samples has shown that self-reported protection corresponds moderately with objective measures of UVR (Glanz et al., 2010), and there is consistency between retrospective reports of protection taken daily, weekly, and three-monthly (i.e., over the summer; Hillhouse, Turrisi, Jaccard, & Robinson, 2012), although self-reports in this context tend to involve frequency of behaviour measures rather than a simple 0-100 scale as was used here.

The DPS was developed to allow for the interpretation of behavioural data and represents a strength of the study. It does, however, only reflect the relative ranking of behaviours and combinations, as opposed to the actual level of protection afforded by different behaviour/s, and has yet to be validated by relevant clinicians outside the UK national XP team. Further, the combinations were ranked and grouped without consideration of whether sunscreen was used, when in practice, this may make a difference to the protection achieved. Similarly, the use of Dermagard on windows was not assessed and so it cannot be assumed that other protective measures were not in place or that participants were necessarily safe from UVR during all indoor time (which was not included in the analysis). The protection associated with the reported behaviours may, therefore, be an underestimation and skin and DNA damage might not actually

result from what appears to be poor protection here. Further, although participants were asked to self-report their protection *only* on the days they had been outside, the protection afforded by staying indoors may have been conflated in self-reports with behavioural protection when outdoors, explaining some of the discrepancies between self-reported protection and satisfaction. Nonetheless, the behaviours involved in photoprotecting (including both the use of clothing and sunscreen, and adapting outdoor time around UVR risk) are the only way that patients with XP can reduce the risks associated with exposure (and will be the target of intervention), so understanding the nuances of this behaviour is important, even if some measurement error remains. While beyond the scope of this paper and not collected for this purpose, the objective measurement of UVR exposure using a wrist-worn dosimeter for another sub-study (Walburn, Sarkany, et al., 2017) will also allow validation of any uncertainties regarding the distinction between indoor and outdoor time, with the combination of UVR dose and behaviour informing the personalized intervention targets.

The lack of previous research in this population and unclear applicability of sun protection research (e.g., Rodrigues et al., 2013) for a rare and high-risk group, combined with the issue of patient burden in a longitudinal design meant that decisions about inclusion of potential predictors were frugally made. This may mean that important drivers of variation in behaviour were missed. Similarly, factors that do not vary over time but nonetheless hold predictive value (e.g., age of diagnosis, geographical location, personality or executive functioning capacity) cannot be included in an intra-individual design, so the picture painted here does not provide a complete guide to the selection of intervention targets or means of tailoring. The benefit of a mixed-methods project is that data from a range of sources can be triangulated and used to fill gaps created by methods that are perhaps not suited or sensitive enough to uncover the complexity of non-adherence for some people (e.g., with qualitative interview findings) to achieve this aim (Johnson & Onwuegbuzie, 2004; Munafo & Davey Smith, 2018; Walburn, Sarkany, et al., 2017).

Finally, the optimal parameters for the conduct, and thresholds for analysis, of an n-of-1 study are not known and are highly dependent on the degree of variability in behaviour and predictors, which often cannot be specified a-priori due to the unstudied nature of the behaviour before collecting the data. A 50-day recording period was chosen here (Vieira et al., 2017), but for some participants who went outside less frequently than once per day, this did not result in sufficient observations. The time over which data was collected and the frequency of measurement (once per day) may therefore have been insufficient to capture variability in some predictors and affected covariation with behaviour. For example, emotional factors are likely to vary even within the course of a day, and so may require a more fine-grained protocol, whereas motivation appeared not to vary much for most people. Nonetheless, the finding of stability for some people on some variables, including protection behaviour, is an important one, rather than necessarily an indication of failing methods. A lack of variability in protection is most clinically relevant for individuals who notoriously and habitually do not protect well; the group for whom intervention is most needed. While we were unable to make recommendations for intervention decisions for these people, it is worth noting that between-participant designs may be equally unable to answer the question of what is likely to lead to change for people with consistently poor protection, with the most appropriate solution being to deliver an intervention and observe how (and via what means) their behaviour changes. Finally, the potential benefits of n-of-1 designs in rare diseases are numerous. It is, however, currently unclear whether interventions based on these methods are more effective than those informed by more traditional between-participant findings, or where intervention targets are selected by extrapolating from research in similar populations and behaviours (e.g., sun protection in other high-risk groups).

Conclusion

XP has no cure and the only treatment available is rigorous photoprotection to reduce UVR-related skin damage. Understanding the complexity of the behaviours involved in achieving this goal is an important first step in the research process to aid intervention design, as well as the self-

management of the condition and clinician approach to treatment. We have demonstrated the utility of an individualized approach, resulting in the identification of differences in protective behaviours used, and the stability and predictors of those behaviours. Consequently, evidence-based recommendations and decisions about the range of possible primary outcomes and additional targets for the intervention, as well as criteria for success, have become possible. In specifying these steps, we hope that researchers in other areas may benefit from applying a similar process to the understanding, definition, profiling, and prediction of poorly-understood complex behaviours to enable much-needed intervention development to flourish in rare diseases.

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